chemical binding] covalent bonding, or noncovalent bonding characteristic of antibody-antigen, specific binding protein-receptor and enzyme-substrate associations, the prosthesis having a valve structure.

REMARKS

Claims 1-11, 14, 15 and 21-28 remain for consideration. Claims 1 and 14 have been amended to more particularly point out Applicants' invention. The amendments to claims 1 and 14 are supported by Applicants' specification, for example, at page 13, lines 17-28 and page 14, lines 9-16. Claim 14 has also been amended to clarify the structure of the prosthesis. No new matter is introduced by the amendments to the claims.

Drawings

The Examiner noted that photographs are only acceptable for examination purposes if a Petition to Accept Photographs is filed and accepted. Applicants have filed formal drawings along with a Petition to Accept Color Photographs. The Petition has been accepted.

The Examiner has objected to the drawings because no detail was discernable in the photograph photocopies submitted for examination. However, actual photographs have been submitted in triplicate to the Patent Office. If the Examiner requires additional information for examination of the case, the Examiner is requested to telephone Applicants' undersigned representative. In view of the submission of actual photographs and the acceptance of Applicants' petition, Applicants respectfully request the withdrawal of the objection to the photographs.

Rejections Over Noishiki

The Examiner rejected claims 14, 21, 22 and 24 under 35 U.S.C. §102(b) as anticipated by European application EP 0742020 to Noishiki (the EP Noishiki application). In particular, the Examiner noted that non-covalent chemical bonding within

Applicants' claims can include ionic bonding, van der Waals bonding, etc. The Examiner asserts that these types of bonding are disclosed in the EP Noishiki application. Applicants respectfully request reconsideration of the rejections over the EP Noishiki application in view of the following comments.

Lack of novelty under 35 U.S.C. §102 requires that every element in the claim at issue is found in a single reference. Minnesota Mining and Manufacturing Co. v. Johnson & Johnson Orthopaedics, Inc., 976 F.2d 1559, 1565, 24 USPQ2d 1321, 1326 (Fed. Cir. 1992). Applicants' claims 14, 21, 22 and 24 are directed to a prosthetic heart valve. To clarify the structure of the heart valve, claim 14 has been amended to indicate that the prosthesis has a valve structure. The EP Noishiki application does not teach or suggest heart valve prostheses or any other valved structure.

Furthermore, the EP Noishiki application does not teach or suggest tissue substrates. The EP Noishiki application, at column 8, lines 47-58 mentions cells and tissues for use as **bioabsorbable substances for incorporation into the pores of a porous substrate**, in particular fabric. The EP Noishiki applications states (emphasis added):

> The bioabsorbable substance(s) can be encapsulated easily by entanglement with porous structure of the prosthesis substrate. For this purpose, **bioabsorbable substances with a filamentous shape or a large size (i.e., cells and tissues)** are preferable, but those with a nonfilamentous shape or small size can also be used. To capture the filamentous substances, **a diluted suspension of the substance or its solution** can be used having a viscosity at 22°C of less than or equal to about 1000 mPa's as measured on a viscosity meter for a **collagen fiber suspension**, the concentration of the collagen can be equal to or less than about 1.0 wt. %.

In context, the EP Noishiki application is referring to dispersed cells and tissue to form collagen fibers and loose cells that can be incorporated into the pores of the fabric substrate. See also column 3, lines 52-58 of the EP Noishiki application. The EP

Noishiki application does not teach or suggest tissue as a **substrate**.

Since the EP Noishiki application does not teach or suggest valved prostheses or tissue substrates, the EP Noishiki application does not anticipate Applicants' claims 14, 21, 22 and 24. Applicants respectfully request the withdrawal of the rejection of claims 14, 21, 22 and 24 under 35 U.S.C. §102(b) as anticipated by the EP Noishiki application.

Rejections Over Bayne et al.

The Examiner rejected claims 1-5 and 9-11 under 35 U.S.C. §102(b) as being anticipated by or, in the alternative, under 35 U.S.C. §103(a) as obvious over EP 0476983 to Bayne et al. (the EP Bayne application). The Examiner cited the EP Bayne application for disclosing fixed umbilical veins coated with proteins and growth factors. Applicants respectfully request reconsideration based on the following comments.

The Examiner asserts that the Bayne application discloses umbilical vein tissue associated with VEGF. Applicants believe that the EP Bayne application only discloses the use of growth factors to stimulate cell cultures of endothelial cells and the association of growth factors with **synthetic** polymer blood vessels. Specifically, **Applicants do not believe that the Bayne application teaches or suggests the association of VEGF with tissue**. This position was asserted in the Amendment of October 7, 1999, but the Examiner did not comment on Applicants' position in the Office Action of January 5, 2000.

The EP Bayne patent describes the use of VEGF II "in the promotion of tissue repair." This discussion is found mainly on page 8 of the EP Bayne application. The EP Bayne application describes the use of VEGF in tissue repair either by using VEGF to promote cell growth in tissue culture or by applying a coating of VEGF to a synthetic polymer material.

First, the EP Bayne application discusses the use of VEGF II to stimulate vascular endothelial cells in cell culture. This is described on page 8, lines 8-19 and 27-29. The **cells** are then plated onto synthetic polymer substrates or fixed umbilical vein for the formation of an artificial blood vessel, see page 8, lines 17-19 and 30-35. **In this cell culture approach, the VEGF is not contacted with the substrate itself.** Once the cells are grown to desired levels in the cell culture, the cells are removed and placed in contact with the inner surface of the synthetic polymer substrate or the fixed umbilical vein.

In the second approach, the EP Bayne application further describes the coating of VEGF II onto a **synthetic polymer support** prior to implantation of the artificial blood vessel into the patient, page 8, lines 20-21. Following implantation, it is speculated that endothelial cells will colonize the artificial surface. See page 8, lines 20-21. The EP Bayne application does not teach or suggest associating VEGF with any type of **tissue**, as described and claimed by Applicants.

Since the EP Bayne application does not teach or suggest associating VEGF with tissue, the EP Bayne application does not anticipate claims 1-5 and 9-11 and does not render Applicants' claimed invention obvious. Applicants respectfully request the withdrawal of the rejection of claims 1-5 and 9-11 under 35 U.S.C. §102(b) as being anticipated by or, in the alternative, under 35 U.S.C. §103(a) as obvious over the EP Bayne application.

Rejections Over Tischer et al. and Orton

The Examiner rejected claims 1, 2, 6, 7, 9-11, 14, 15, 21 and 22 under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent 5,194,596 to Tischer et al. (the Tischer patent) in view of U.S. Patent 5,192,312 to Orton (the Orton patent). In particular, the Examiner cited the Tischer patent for disclosing soaking a transplant with VEGF prior to implantation. The Examiner cited the Orton patent for disclosing allograft and xenograft tissues for use

in forming growth factor treated tissue. Applicants have amended claims 1 and 14 to more distinctly claim their invention. Applicants respectfully request reconsideration of the rejections over Tischer and Orton in view of the following comments.

The Tischer patent discloses the application of VEGF in a carrier material to a vascular graft. See, for example, column 12, lines 8-16. The Orton patent describes the soaking of a graft in a solution with a growth factor. The graft is then placed into a cell culture. See, for example, column 6, lines 2-7. The Tischer patent and the Orton patent do not teach or suggest the association of VEGF or other growth factors with a substrate using a biologic glue, covalent bonding, or noncovalent bonding characteristic of antibody-antigen, specific binding protein-receptor and enzyme substrate associations. Since the Tischer patent and the Orton patent do not teach or suggest the claimed approaches for associating VEGF with the substrate, the combined disclosures of the Tischer patent and the Orton patent do not render Applicants' claimed invention obvious.

Due to the deficiencies of the disclosures of the Tischer patent and the Orton patent, Applicants respectfully request the withdrawal of the rejection of claims 1, 2, 6, 7, 9-11, 14, 15, 21 and 22 under 35 U.S.C. §103(a) as being unpatentable over the Tischer patent in view of the Orton patent.

Rejections Over Tischer et al., Orton and Carpentier et al.

The Examiner rejected claims 8 and 23-28 under 35 U.S.C. §103(a) as being unpatentable over the Tischer patent and the Orton patent as applied above, and further in view of U.S. Patent 4,648,881 to Carpentier et al. (the Carpentier patent). The Examiner noted that the Tischer patent and the Orton patent failed to disclose pericardial tissue or crosslinked tissue. The Examiner cited the Carpentier patent for disclosing bovine pericardial tissue and crosslinked tissue for constructing heart valves.

Applicants respectfully request reconsideration of the rejection of claims 8 and 23-28 based on the following discussion.

With respect to claim 8, Applicants have amended claim 1, from which claim 8 depends, to more distinctly claim their invention. Similarly, with respect to claims 23 and 24 which depend from claim 14, Applicants have amended claim 14 to more distinctly claim their invention. As noted above, the Tischer patent and the Orton patent do not teach or suggest the association of VEGF or other growth factors with a substrate using a biologic glue, covalent bonding, or noncovalent bonding characteristic of antibody-antigen, specific binding protein-receptor and enzyme substrate associations. The Carpentier patent does not teach or suggest growth factors. Thus, the Carpentier patent does not make up for the deficiencies of the Tischer patent and the Orton patent. Since the Tischer patent, the Orton patent and the Carpentier patent do not teach or suggest the claimed approaches for associating the growth factor with the substrate, the patents collectively do not render claims 8, 23 and 24 obvious.

With respect to claims 25-28, Applicants do not believe that the references motivate the combination suggested by the Examiner. "There must be some reason, suggestion, or motivation found in the prior art whereby a person of ordinary skill in the field of the invention would make the combination. That knowledge cannot come from the applicant's invention itself." In re Oetiker, 24 USPQ2d 1443, 1446 (Fed. Cir. 1992). A combination of references does not establish prima facie obviousness absent a suggestion for the combination in the references or in the general knowledge of a person of skill in the art. In re Jones, 21 USPQ2d 1941, 1943, 1944 (Fed. Cir. 1992). Furthermore, prior art renders a claim obvious only if it conveys to a person of ordinary skill in the art a reasonable expectation of success in practicing the claimed invention. In re Vaeck, 20 USPQ2d 1438, 1442, 1443 (Fed. Cir. 1991).

The Carpentier patent notes that glutaraldehyde crosslinking is associated with significant calcification that reduces the useful lifetime of the prosthesis. See the Background of the Carpentier patent. The Carpentier patent discloses reduction of the calcification. Crosslinking or fixation is performed on xenografts to reduce antigenicity. Then, xenografts can be used as alternatives to allografts. See column 1, lines 10-11. If fixed or crosslinked tissue is used, immunosuppressants generally are not needed. However, the Orton patent discloses the killing and/or removal of native cells using approaches other than fixation, in particular, x-rays, antibiotics, antibacterials or cytotoxic agents in lethal doses. See column 5, lines 53-63. A new population of cells is introduced in a cell culture. See column 6, lines 2-7. According to the Orton patent, "an adverse immune response and ultimately graft rejection can be minimized or avoided." Column 6, lines 5-7. Since the Orton patent discloses alternatives to crosslinking to remove undesirable immune responses, there would be no motivation based on the teachings of the Carpentier patent and the Orton patent to crosslink the tissue prior to performing the Orton procedure.

Furthermore, the Tischer patent does not describe any details about the vascular grafts other than to indicate that they can be "transplanted vessels or synthetic material." See column 11, lines 65-69. Synthetic materials are not relevant to claims 25-28. Transplanted vessels would seem to suggest allograft or autograft tissue. Allograft and autograft tissue is not necessarily crosslinked since crosslinked creates a risk of calcification. Since the Tischer patent does not disclose the types of tissue that generally are crosslinked, the Tischer patent would not provide any teaching that would suggest the desirability of using crosslinked tissue. Thus, there is no motivation to combine the teachings of the Carpentier patent with the Tischer patent.

Since the Orton, Tischer and Carpentier references do not motivate the association of growth factors with crosslinked tissue, the cited references do not render obvious Applicants' claims 25-28 relating to crosslinked tissue.

Applicants respectfully request the withdrawal of the rejection of claims 8 and 23-28 under 35 U.S.C. §103(a) as being unpatentable over the Tischer patent and the Orton patent as applied above, and further in view of the Carpentier patent.

CONCLUSIONS

In view of the foregoing amendments and remarks, Applicants submit that the application is in condition for allowance, and such action is respectfully requested. The Examiner is invited to telephone the undersigned attorney to discuss any questions or comments that the Examiner may have.

The Director of the Patent Office is authorized to charge any fee deficiency required by this paper or credit any overpayment to Deposit Account No. 23-1123.

Respectfully submitted,

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